Death from stroke in end-stage kidney disease

Death from stroke in end-stage kidney disease: a population-based study using data linkage

Cover title: Death from stroke: ESKD vs general population

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Abstract

Background: People with end-stage kidney disease (ESKD) are at greater risk of stroke. We aimed to compare stroke mortality between the ESKD population and the general population.

Methods: We included all incident ESKD patients in Australia, 1980-2013 and New Zealand, 1988-2012. The primary cause of death was ascertained using data linkage with national death registers. We produced standardized mortality ratios (SMR) for stroke deaths, by age, sex and calendar year.

Results: We included 60,823 ESKD patients, where 941 stroke deaths occurred over 381,874 person-years. ESKD patients had >3 times the stroke deaths compared to the general population (SMR:3.4, 95%CI:3.2-3.6), markedly higher in younger people and females. The greatest excess was in intracerebral haemorrhages (SMR:5.2, 95%CI:4.5-5.9). Excess stroke deaths in ESKD patients decreased over time, though was still double in 2013 (2013 SMR:2.1, 95%CI:1.5-2.9).

Conclusions: People with ESKD experience much greater stroke mortality with the greatest difference for women and younger people. However, mortality has improved over time.

Introduction

People with end-stage kidney disease (ESKD) are at greater risk of stroke, with stroke-hospitalizations 2-3 times that of the general population [1]. Despite the increased risk of stroke, how ESKD affects stroke mortality remains unclear. Limited trial data suggests some interventions are less effective in ESKD patients, where statin therapy and warfarin have little to no effect on reducing stroke events [2, 3]. We aimed to compare stroke mortality rates for the ESKD population versus the general population, using a population-based approach.

Method

Study data are available to qualified researchers from the corresponding author, subject to study and ethical approvals.

Participants, data linkage and death outcomes

We used prospective observational data collected in the Australian and New Zealand Dialysis and Transplant (ANZDATA) Registry, which includes all people with ESKD from initiation of ESKD treatment. Nationwide summary-level data was used to determine stroke mortality rates in the general population in Australia and in New Zealand. Both countries provided the number of deaths by underlying cause of death using ICD-10-AM, sex, 5-year age band and calendar year.

We used data linkage of ANZDATA to the national death registers to ascertain date and cause of death. We linked Australian ESKD patients using probabilistic record linkage and New Zealand ESKD patients using deterministic record linkage. Due to limited data in the national death registers, we only included incident ESKD patients in Australia, 1980-2013 and in New Zealand, 1988-2012.

Stroke deaths were determined from the underlying cause of death only using ICD-10-AM codes. All other causes of death were considered as non-stroke deaths.

Statistical analyses

Patient follow-up was from ESKD treatment date until the earliest date of; death, 31 December 2013 (Australia) or 31 December 2012 (New Zealand). We produced mortality rates and standardized mortality ratios (SMR). The overall cumulative incidence of stroke mortality was estimated by summing to time *t* the Kaplan-Meier estimate of the overall survival function, *S(t-1),* multiplied by the subtype hazard at time *t*.

Ethical approval was granted from the University of Sydney (Project:2014/917), AIHW (Ref:EO2015/3/181) and the New Zealand Ministry of Health (Ref:14/NTB/171).

See Supplemental Methods for further methodological details.

Results

Patient Characteristics

We included 60,823 incident ESKD patients, where death agreement between ANZDATA and the national death registry was almost perfect (Kappa statistic: 0.85; Supplementary Table 1). There were 26,505 (41%) patients still alive and 34,318 (59%) patients had died (Supplementary Fig.1). There were 941 stroke deaths over 381,874 person-years follow-up, with median follow-up of 4 years (Supplementary Table 2).

Deaths

Of the 941 stroke deaths, there were 259(27%) intracerebral haemorrhages, 90(10%) intracranial haemorrhages, 108(12%) ischaemic strokes, 68(7%) subarachnoid haemorrhages, 302(32%) unspecified strokes and, 114(12%) transient cerebral ischaemic attacks and related syndromes. The cumulative incidence of all-cause stroke mortality was 1.4%(95%CI:1.3-1.6%) in females and 1.0%(95%CI:0.9-1.1%) in males at 5 years (Fig.1).

Stroke mortality rates

Overall, the crude mortality rate for all-cause stroke was 246.4(95%CI:231.2-262.7)/100,000person-years. The all-cause stroke mortality rates showed a clear increasing trend with age for both sexes (Supplementary Fig.2A). However, there was little evidence of a trend or sex difference for mortality rates in ischaemic strokes and intracerebral haemorrhages (Supplementary Fig.2B-2C).

The all-cause stroke mortality showed a slight decreasing trend in more recent years. The all-cause stroke mortality rate per 100,000 person-years decreased from 245.7(95%CI:132.2-456.7) in 1988 to 194.4(95%CI:146.1-258.8) in 2011. There was little evidence of a consistent pattern for stroke mortality rates over calendar year for ischaemic strokes or intracerebral haemorrhages.

Stroke mortality standardized mortality ratios (SMR)

The all-cause stroke SMR was 3.4(95%CI:3.2-3.6), ischaemic stroke was 3.1(95%CI:2.6-3.7) and intracerebral haemorrhages was 5.2(95%CI:4.5-5.9). The all-cause stroke SMR were greater in younger age and for females (Fig.2A; Supplementary Table 3). These SMR decreased with age, where stroke mortality rates in the ESKD population were comparable to

the general population when aged>75 years. The SMR for ischaemic strokes and intracerebral haemorrhages followed a similar trend (Fig.2B-2C; Supplementary Table 3).

The all-cause stroke SMR decreased over time (Fig.3A). The SMR were highest in 1988-1998, where the SMR reduced from 4.1(95%CI:2.9-5.6) in 1998 to 2.1(95%CI:1.5-2.9) in 2013. Since 2000, the intracerebral haemorrhage SMR have stabilized around 5(2013: 5.2 SMR, 95%CI:3.1-8.8; Fig.3B). Ischaemic stroke SMR were substantially varied prior to 1998, after which SMR were relatively stable at <5 (2013: 1.7 SMR, 95%CI:0.7-4.6; Fig.3C).

Discussion

Our work represents the largest cohort study to date examining stroke death in people with ESKD. Over 30 years, in a dual-national comparison, people with ESKD had more than threefold increased risk of stroke death compared to age and sex-matched people in the general population, predominantly from haemorrhagic stroke. The relative risk of stroke death was highest for younger people and females. Although stroke death rates have decreased rapidly in people with ESKD, the risk of stroke death in 2013 was still double that of the general population.

We found stroke deaths were more likely in people with ESKD compared to the general population, being greater for intracerebral haemorrhage than ischaemic stroke. Admission stroke severity and post-stroke neurological deterioration increases progressively as estimated glomerular filtration rate decreases [4]. Preventative interventions may be ineffective in the ESKD population. Antithrombotic agents in people with ESKD are associated with increased bleeding and cardiovascular mortality, lacking evidence in reducing stroke incidence [3, 5]. Stroke thrombolysis in people with CKD is associated with an increased risk of haemorrhagic

transformation and mortality [6]. ESKD-specific factors may also increase bleeding risk, such as frequent anticoagulation with heparin (on haemodialysis) and uraemia-induced impaired platelet function. One study found that 35% of haemorrhagic strokes occurred during or within 30 minutes after haemodialysis [7]. Dialysis patients are also less likely to be managed in an acute stroke unit and receive post-stroke care compared to patients without CKD [8]. Secondly, age and sex varied the risk of stroke death in people with ESKD. Younger people experienced up to 15 times the stroke deaths than expected. This suggests the greatest potential benefit for stroke interventions is amongst the young [9]. The relative protective effect of being female seen in the general population for Australia and New Zealand, where women have 20-30% lower risk of stroke death, is lost in ESKD. Women with ESKD reach menopause 5 years earlier than people without ESKD and are frequently amenorrheic at ESKD diagnosis, losing the protective effect of oestrogen earlier than expected [10]. Stroke prevention strategies may be implemented less often in women and sex differences in the setting of post-stroke care may exist [11].

Finally, excess stroke deaths in the ESKD population decreased over time, particularly in 1998-2003. An increased prevalence of kidney transplants which are associated with reduced cardiovascular risk compared to dialysis, better transplant survival and increased living kidney donation may all contribute to this reduction in risk [12].

There are several limitations to our study. The primary cause of death was ascertained from the national death register only, which does not capture overseas deaths, although typically people with ESKD are not internationally mobile. Large confidence intervals occurred when stratum-specific sample sizes or general population mortality rates were low, evident in

younger age bands and <1997. We were limited to the patient treatment data recorded by ANZDATA, where the use of primary or secondary stroke prevention drugs is not recorded.

In conclusion, we found that all-cause stroke deaths were >3 times higher in the ESKD population than expected. Further research is needed into stroke prevention, treatment and care provided to ESKD patients, particularly in females and younger ESKD. Future studies explicitly including people with ESKD is required to evaluate the effectiveness, tolerability and safety of stroke prevention drugs and treatment. A better understanding of the current use of stroke prevention and care following stroke in the ESKD population would be useful to determine whether further improvements are possible.

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Disclosures

None.

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Figure 1. Cumulative incidence of all-cause stroke mortality in people with end-stage kidney disease, by gender.

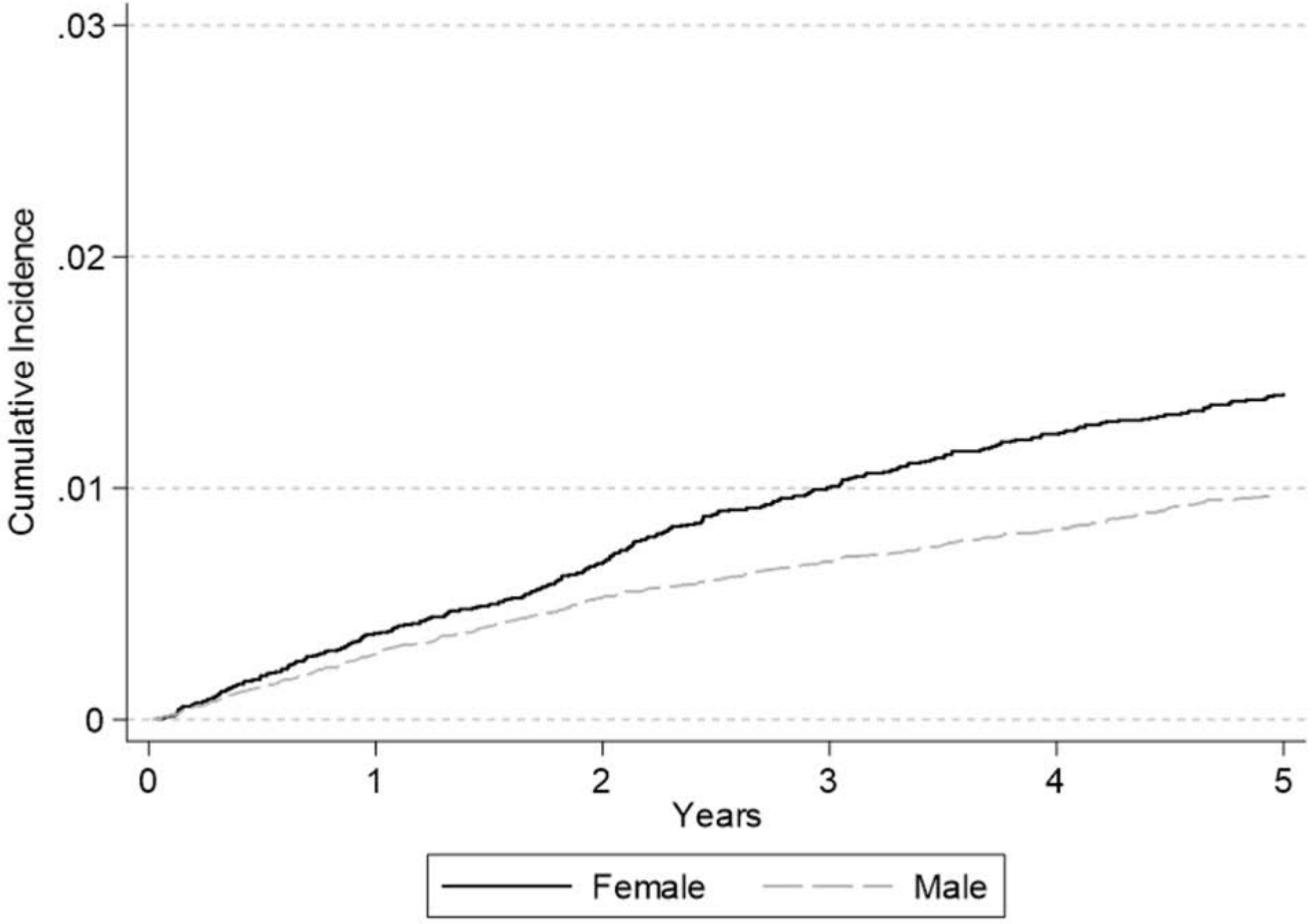
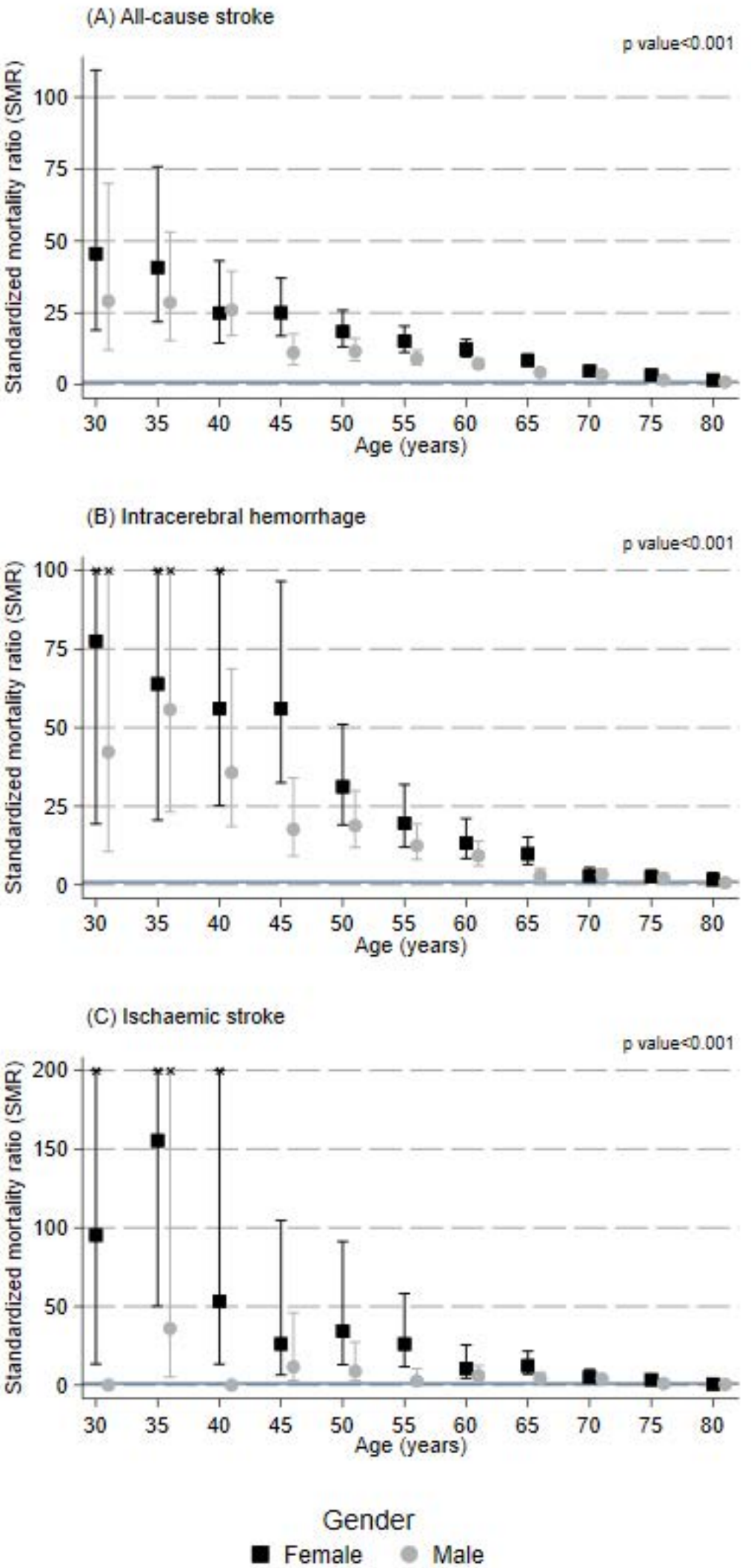
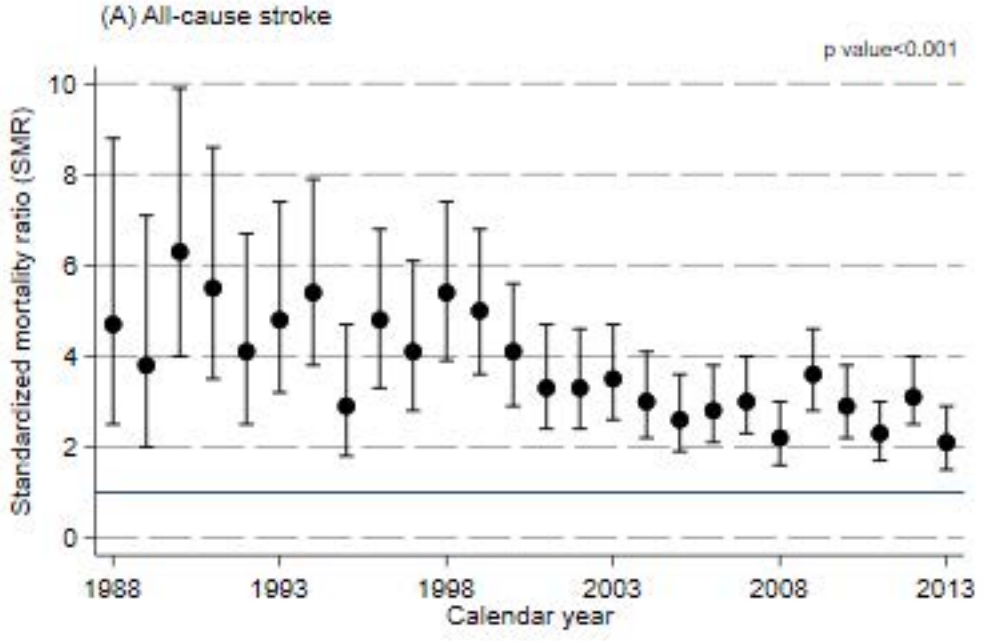


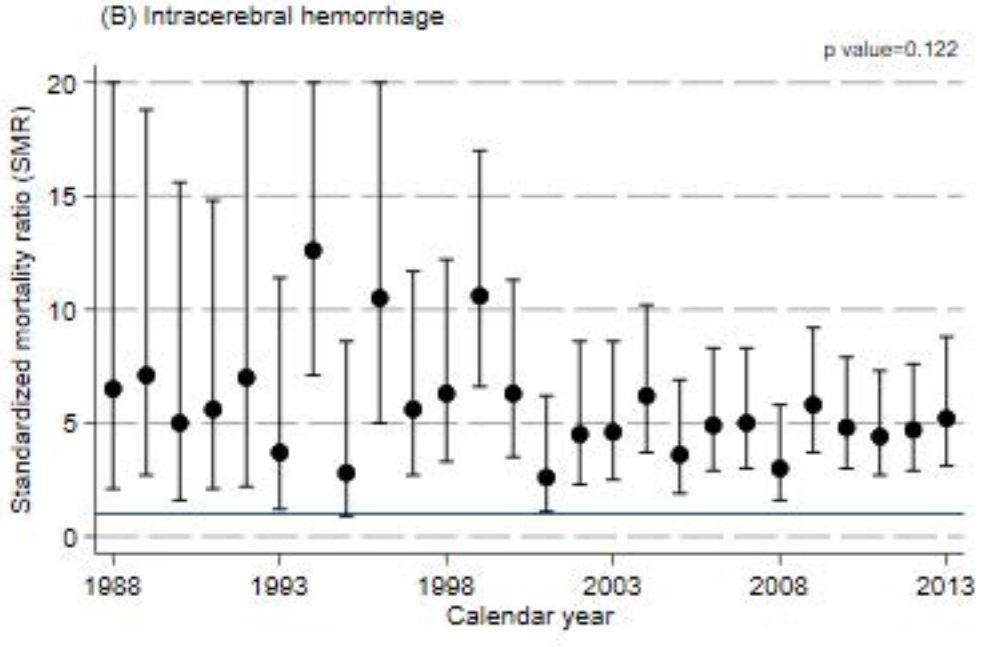
Figure 2. Standardized mortality ratios (SMR) for people with end-stage kidney disease, stratified by age and sex, in: (A) all-cause strokes; (B) intracerebral haemorrhages; (C) ischaemic strokes.

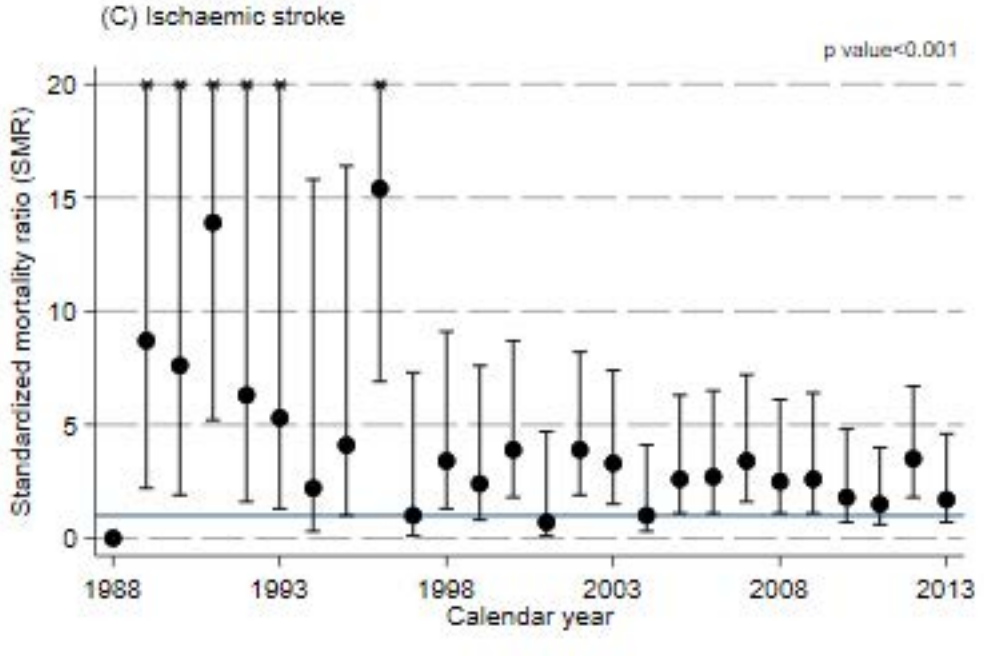


Note: P-values are test for trend across age groups.

Figure 3. Standardized mortality ratios (SMR) for people with end-stage kidney disease, stratified by calendar year, in: (A) all-cause strokes; (B) intracerebral haemorrhages; (C) ischaemic strokes.







Note: P-values are test for trend across age groups.

SUPPLEMENTAL MATERIAL

Supplemental Methods

People with ESKD: We used observational patient data collected prospectively in the Australian and New Zealand Dialysis and Transplant (ANZDATA) Registry, which includes all people treated for ESKD from 1964 in Australia and New Zealand. ANZDATA data collection methods and validation have been previously described [1]. Briefly, all dialysis and transplant centres in Australia and New Zealand provide data on all people with ESKD from initiation of ESKD treatment. People with ESKD included any person who was receiving renal replacement therapy, including haemodialysis, peritoneal dialysis and kidney transplant. Patient data is collected via web-based data entry or printed survey forms as events occur, and annually, for each ESKD patient. The core patient data collected include: demographics (date of birth; sex; racial background; body mass index; and smoking status), co-morbidities (diabetes; ischaemic heart disease; cerebrovascular disease; coronary artery disease; peripheral artery disease; and malignancies) and ESKD history (dialysis modality; data of treatment initiation; and cause of ESKD).

General population: We used nationwide summary-level data that was publicly available to determine stroke mortality rates in the general population in Australia and New Zealand. In Australia, the Australian Bureau of Statistics provides publicly available data on the number of deaths by underlying cause of death using ICD-10-AM, sex, 5-year age bands and calendar year. In New Zealand, the New Zealand Ministry of Health provides data tables on registered deaths occurring in New Zealand, stratified by underlying cause of death using ICD-10-AM, sex, 5-year age bands and calendar year.

Data linkage: We used data linkage of ANZDATA to the national death registries to ascertain date and causes of death, both underlying and contributing causes. In Australia, the National Death Index (NDI) records all deaths from 1980 and is maintained by the Australian Institute of Health and Welfare (AIHW). We linked Australian ESKD patients using probabilistic record linkage, matching on date of birth, sex and full name. In New Zealand, the Mortality Collection (MORT) Database records all deaths from 1988 and is maintained by the New Zealand Ministry of Health. We linked New Zealand ESKD patients using deterministic record linkage, matching on the national health index (NHI) number. In this analysis, we were restricted to data available in the national death registries. Hence, we included all incident ESKD patients in Australia, 1980-2013 and in New Zealand, 1988-2012.

Data linkage were undertaken by the AIHW, and New Zealand Ministry of Health using best-practice privacy-preserving protocols. Only de-identified data was provided after data linkage was complete.

Death ascertainment and cause of death: ESKD patient deaths were ascertained from the national death registries only. Stroke deaths were determined from the declared underlying cause of death only, using ICD-10-AM codes. Underlying causes of deaths are defined as the disease or condition which initiated the sequence of events that resulted in the patients' death. Where contributory causes of death included stroke, but the underlying cause of death listed another cause, an individual was deemed to have died a non-stroke death. Contributing or secondary causes of death are all other diseases or conditions that contributed to the death but were not the underlying cause. Specifically, all-cause stroke deaths included subarachnoid haemorrhage

(I60.0-I60.9), intracerebral haemorrhages (I61.0-I61.9), intracranial haemorrhages (I62.0-I62.9), ischaemic strokes (I63.0-I63.9), unspecified strokes (I64.0-I64.9) and, transient cerebral ischaemic attacks and related syndromes (G45.0-G45.9). Subtype stroke deaths of interest included intracerebral haemorrhages and ischaemic strokes. All other causes of death were considered as non-stroke deaths. The causes of death were summarized using the leading causes of death, modified by AIHW [2].

Statistical analyses

Patient follow-up was from ESKD treatment date until the earliest date of; death, 31 December 2013 (Australian only) or 31 December 2012 (New Zealand only). As probabilistic record linkage could lead to a small proportion of incorrect links [3], Australian ESKD patients with discordant records were censored at the ANZDATA date of death when the national death registry had not captured any death. We used the Kappa statistic to evaluate agreement of fact of death [4].

Crude mortality rates were produced for all-cause and subtype stroke deaths by dividing the number of stroke deaths by the total follow-up time where patients were at risk of stroke, by age, sex, and calendar year. We used indirect standardization to produce standardized mortality ratios (SMR). Briefly, all-cause and subtype stroke crude mortality rates were calculated for the general population in Australia and New Zealand, by age, sex and calendar year. For the general population, the numerator was considered as the total stroke deaths and the denominator was the population total for the given calendar year, sex and 5-year age band. The general population stroke mortality rates were then applied to the person-years of follow-up in the ESKD population to estimate the expected number of all-cause and subtype stroke deaths. The SMR were then estimated as the ratio between the sum of observed deaths and the expected deaths. A test for linear trend for age and calendar year were performed on the SMR.

Data were analysed using Stata version 14 (Stata Corporation, College Station, TX, USA).

Supplementary Table 1. Agreement for fact of death between ANZDATA and national death registries.

(A) Overall[1]				
		Death Registry		**Total**
		Dead	**Alive**	
ANZDATA	**Dead**	34 206 (56)	1 623 (3)	35 829
	Alive	2 823 (5)	22 171 (36)	24 994
Total		37 029	23 794	60 823 (100)
(B) Australia[2]				
		Death Registry		**Total**
		Dead	**Alive**	
ANZDATA	**Dead**	28 880 (56)	1 106 (2)	29 986
	Alive	2 823 (5)	18 642 (36)	21 465
Total		31 703	19 748	51 451 (100)
(C) New Zealand[3]				
		Death Registry		**Total**
		Dead	**Alive**	
ANZDATA	**Dead**	5 326 (57)	517 (6)	5 843
	Alive	0 (-)	3 529 (38)	3 529
Total		5 326	4 046	9 372 (100)

[1]Overall agreement for fact of death was 92.7% with Kappa statistic of 0.85 (p-value <0.001).
[2]Overall agreement for fact of death was 92.4% with Kappa statistic of 0.84 (p-value <0.001).
[3]Overall agreement for fact of death was 94.5% with Kappa statistic of 0.89 (p-value <0.001).

Supplementary Table 2. Characteristics of all patients with end-stage kidney disease included in the study, stratified by death status.

Characteristics	All-cause stroke deaths		Other deaths		Alive		Total	
	n	(%)[1]	n	(%)[1]	n	(%)[1]	n	(%)[1]
Total, (%)	941	(2)[2]	33,377	(55)[2]	26,505	(43)[2]	60,823	(100)
Age at ESKD diagnosis (years)								
≤29	25	(3)	1,150	(3)	3,913	(15)	5,088	(8)
30-49	177	(19)	5,399	(16)	8,231	(31)	13,807	(23)
50-64	329	(35)	11,417	(34)	8,234	(31)	19,980	(33)
65-74	261	(28)	9,658	(29)	3,923	(15)	13,842	(23)
≥75	149	(16)	5,753	(17)	2,204	(8)	8,106	(13)
Median [IQR]	62	[52, 71]	63	[53, 72]	51	[38, 63]	59	[46, 69]
Gender								
Female	472	(50)	13,901	(42)	10,669	(40)	25,042	(41)
Male	469	(50)	19,476	(58)	15,836	(60)	35,781	(59)
Year of ESKD								
≤1990	209	(22)	6,269	(19)	1,770	(7)	8,248	(14)
1991-1999	297	(32)	10,637	(32)	3,819	(14)	14,753	(24)
2000-2009	382	(41)	14,561	(44)	11,401	(43)	26,344	(43)
2010-2013	53	(6)	1,910	(6)	9,515	(36)	11,478	(19)
Country								
Australia	819	(87)	28,173	(84)	22,459	(85)	51,451	(85)
New Zealand	122	(13)	5,204	(16)	4,046	(15)	9,372	(15)
Racial background								
Caucasian	737	(78)	26,290	(79)	19,003	(72)	46,030	(76)
Non-caucasian	204	(22)	7,087	(21)	7,502	(28)	14,793	(24)
Comorbidities at ESKD								
Cerebrovascular disease	246	(26)	5,393	(16)	2,037	(8)	7,676	(13)
Diabetes	313	(33)	12,863	(39)	8,541	(32)	21,717	(36)
Coronary artery disease	372	(40)	14,310	(43)	6,103	(23)	20,785	(34)
Peripheral artery disease	252	(27)	9,487	(28)	3,634	(14)	13,373	(22)
Previous malignancy	208	(22)	9,707	(29)	5,873	(22)	15,788	(26)
Smoking status								
Current/Former	413	(44)	16,081	(48)	11,895	(45)	28,389	(47)
Never	345	(37)	11,955	(36)	13,561	(51)	25,861	(43)
Unknown	183	(19)	5,341	(16)	1,049	(4)	6,573	(11)
Cause of renal failure								
Diabetes	249	(26)	9,925	(30)	6,735	(25)	16,909	(28)
Hypertension/renal artery disease	169	(18)	4,763	(14)	2,332	(9)	7,264	(12)
Glomerulonephritis/IgA nephropathy	211	(22)	7,626	(23)	8,795	(33)	16,632	(27)
Polycystic kidney disease	71	(8)	1,623	(5)	2,309	(9)	4,003	(7)
Other	241	(26)	9,440	(28)	6,334	(24)	16,015	(26)
Transplanted at beginning of study	4	(<0.5)	151	(<0.5)	1,494	(6)	1,649	(3)
Transplanted during study	154	(16)	4,997	(15)	11,051	(42)	16,202	(27)

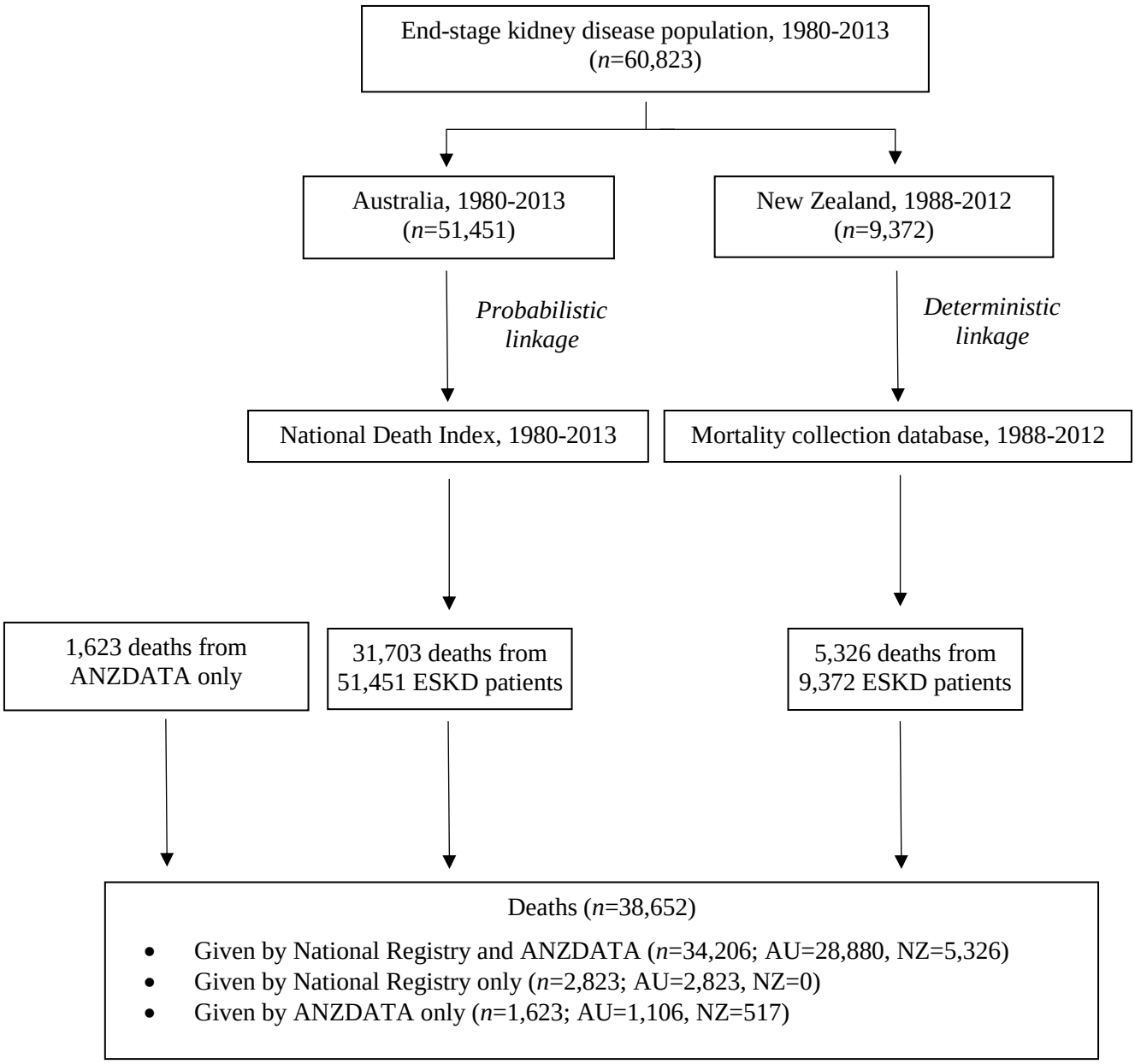
[1]Column percentage; [2]Row percentage.

Supplementary Table 3. Standardized mortality ratios (SMR) in the end-stage kidney disease population compared to the general population for all-cause stroke and stroke subtype, by sex and age.

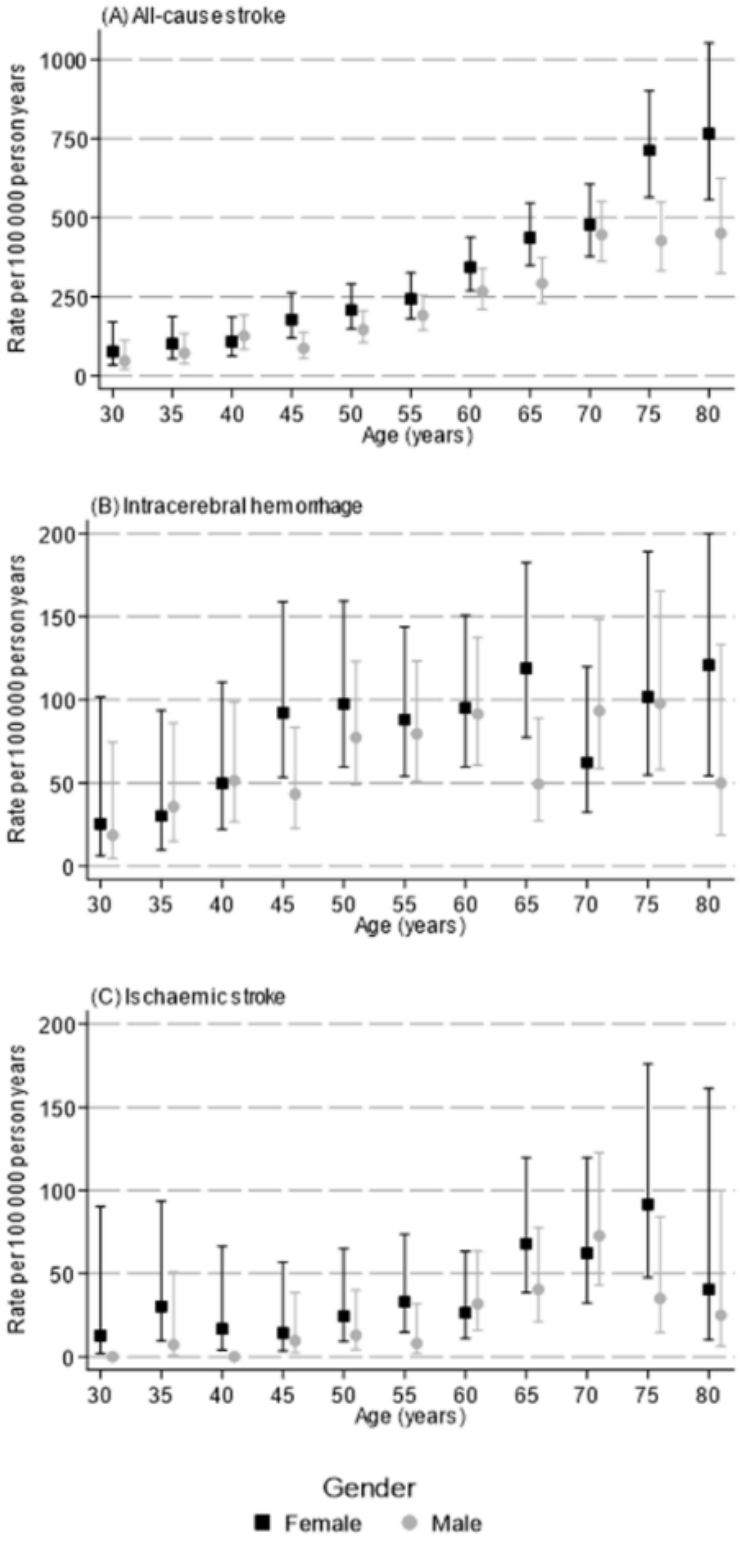
	O	E	SMR(95% CI)	O	E	SMR(95% CI)
Age at death(years)	*30-49*			*50-64*		
Male						
Any stroke death	55	3.0	18.5(14.2, 24.0)	149	17.4	8.6(7.3, 10.1)
Intracerebral haemorrhage	25	0.9	27.9(18.8, 41.3)	61	5.0	12.1(9.4, 15.6)
Ischaemic stroke	3	0.3	10.5(3.4, 32.6)	13	2.4	5.4(3.1, 9.3)
Unspecified stroke	8	0.2	46.1(23.1, 92.3)	27	2.8	9.6(6.6, 14.0)
Female						
Any stroke death	53	1.9	28.3(21.6, 37.1)	143	10.0	14.4(12.2, 16.9)
Intracerebral haemorrhage	24	0.4	58.3(39.1, 87.0)	50	2.7	18.6(14.1, 24.6)
Ischaemic stroke	8	0.1	55.7(27.9, 111.4)	15	0.8	18.3(11.1, 30.4)
Unspecified stroke	5	0.1	58.2(24.2, 139.8)	34	1.1	31.0(22.1, 43.4)
Age at death (years)	*65-74*			*75+*		
Male						
Any stroke death	151	40.6	3.7(3.2, 4.4)	112	110.5	1.0(0.8, 1.2)
Intracerebral haemorrhage	29	9.3	3.1(2.2, 4.5)	19	16.5	1.2(0.7, 1.8)
Ischaemic stroke	23	5.6	4.1(2.7, 6.2)	10	14.4	0.7(0.4, 1.3)
Unspecified stroke	51	12.5	4.1(3.1, 5.4)	58	63.0	0.9(0.7, 1.2)
Female						
Any stroke death	146	23.5	6.2(5.3, 7.3)	127	71.0	1.8(1.5, 2.1)
Intracerebral haemorrhage	30	5.3	5.7(4.0, 8.2)	19	9.9	1.9(1.2, 3.0)
Ischaemic stroke	21	2.7	7.7(5.0, 11.8)	14	8.6	1.6(1.0, 2.7)
Unspecified stroke	55	6.8	8.1(6.2, 10.5)	64	42.9	1.5(1.2, 1.9)

O: Observed; E: Expected; SMR: Standardized mortality ratio; 95%CI:95% Confidence interval

Supplementary Figure 1. Flowchart of data linkage process between the end-stage kidney disease population and the national death registries in Australia and New Zealand.



Supplementary Figure 2. Crude mortality rates in people with end-stage kidney disease, stratified by age and sex, in: (A) all-cause strokes; (B) intracerebral haemorrhages; and, (C) ischaemic strokes.



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